Evolving roles for lung cancer radiation therapy

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Technological advances in and increased availability of radiation therapy, along with the changing demographics of lung cancer, are producing advances in lung cancer radiotherapy.[1] Shifting patterns in lung cancer survival have led to recent calls for a renewed emphasis on radiotherapy for older patients. Lung cancer mortality has decreased among patients younger than 50 years, but it continues to increase among those older than 70 years.[2-3] Lung cancer remains a leading cause of cancer mortality in the United States and around the world, and more than two-thirds of lung cancer cases are diagnosed when the patient is 65 or older.[2-3]

Radiation therapy can be curative for lung tumors, especially when they are diagnosed in early, localized stages. For elderly patients, the 10- to 20-year latency period between radiation exposure and the onset of secondary cancers and heart disease means that the risk-to-benefit ratio is more favorable than might be the case with younger patients.[4-5]

Secondary cancer risks aside, the primary risk of radiation therapy for lung cancer—as with most cancers—has long been the toxic effects of radiation to healthy tissues. Impaired lung function has been the inevitable downside of radiation therapy approaches to cancer treatment.

"The only problem in radiotherapy is minimizing the side-effects," Dr Christian Siedschlag (Netherlands Cancer Institute Radiotherapy Department, Amsterdam) told an audience at the second European Lung Cancer Conference (Geneva, Switzerland, April 28-May 1, 2010). "If one could hit the tumor with arbitrarily high doses without having to worry about (patient) complications, all tumor cells could be killed with 100% certainty."

Recent advances in the timing and targeting of radiation therapy promise to help minimize the "collateral damage" radiotherapy inflicts on healthy tissues—trends that were on display at the second European Lung Cancer Conference. More than 1,600 attendees learned about advances in gene therapies aimed at preventing the spread of lung cancer to other organs, chemotherapeutic advances—and the rapidly evolving role of radiation therapies.

A central theme of the conference was how best to address the need to maintain lung function while aggressively attacking tumor tissue.

"The ultimate aim is to precisely irradiate the target and protect the surrounding tissues from radiation," Dr Corina Udrescu (Centre Hospitalier Lyon Sud, Lyon, France) told conference-goers. "Then we get the optimal ratio of tumor benefit to normal tissue damages."

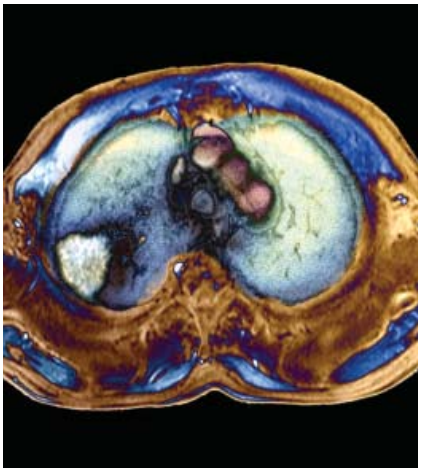
TIMING AND FRACTIONATION

How a given total target radiation dose is administered can be modified by altering fractionation of the dose—changing the number of irradiation sessions and the fraction of the dose delivered at each session. Hyperfractionated (or accelerated) radiotherapy involves administering smaller doses more frequently, giving tumor tissue less time to recover or to develop reduced radiosensitivity.

Randomized studies of survival benefits of hyperfractionation in lung cancer radiotherapy have yielded contradictory results. But pooling study data from 10 trials confirmed a modest overall 5-year survival benefit of 3% for patients with both non-small cell and small cell lung cancers, conference-goers heard from Dr Cecile Le Pechoux (Institut Gustave Roussy, Villejuif, France).

The findings will not yield immediate changes in clinical practice, but they will spark new research into optimized fractionation schedules, Dr Le Pechoux suggested. "Interest in modified fractionation was uncertain before the meta-analysis," she said. "[The] current results will lead to renewed interest in this research field."

Dr Le Pechoux also reported a new meta-analysis comparing combined (concomitant) versus sequentially-administered radio-chemotherapy for locally advanced non-small cell lung cancer.[6] Pooling data from six studies,



An FDG-PET scan shows cancer of the right lung.

the meta-analysis suggested that simultaneous radio-chemotherapy improved 3- and 5-year survival times by 5.7% and 4.5%, respectively, over sequential radiation and chemotherapy–apparently because of improved control of local and regional tumor growth.[6] Unfortunately, metastasis to distant sites was not affected, and local tumor control benefits came at the cost of significantly increased rates of acute, grade 3 to 4 esophageal toxicity (from 4% to 18% of patients).[6]

IMPROVED TARGETING

Larger tumors require higher radiation doses at both isocenters and peripheries, making it more difficult to minimize dose to healthy tissues around target volume margins.[7] Strategies for precise targeting of tumor tissues to limit "collateral" irradiation of nontarget tissue were presented at the European Lung Cancer Conference.

Advances in respiratory gating Respiratory motion of lung tissue moves tumors as well, complicating radiotherapy targeting. Two tools were presented for more precisely targeting moving tumor tissue.

> CT can be used to visualize a tumor's position in different respiratory phases.

Dr Udrescu presented evidence that real-time x-ray imaging with ExacTrac SV during radiotherapy allows adjustment for position and shape changes in lung and liver tumors during irradiation sessions and, hence, better targeting of tumors.

Software improvements for breathing-adapted radiotherapy (BART) were described and reviewed by Dr Nicolas Peguret (University Hospital, Geneva). BART delivers "gated" radiation during specified phases of the respiratory cycle to minimize irradiation of healthy lung tissue. But identifying the optimal treatment phase of respiration for a particular patient has proven challenging, Dr Peguret said. He presented radiotherapy planning software that uses CT to help visualize tumor position in different phases of respiration.

Cold spots Dr Siedschlag presented preliminary data from the Netherlands suggesting that metabolic imaging of tumors with positron emission tomography (PET) using the radioactively-labeled sugar fluorodeoxyglucose-18 (FDG-PET) allows identification of fast- and slow-growing portions of a tumor and, hence, improved precision in radiation dose planning. Because glucose is consumed more rapidly by metabolically active tumor cells (and because tumor cells are growing at a faster rate than healthy cells), the fastest-growing regions of a tumor show up in FDG-PET scans as bright spots—typically, as a bright sphere that is brightest in the center. But when tumors appear "donut-shaped" with a cold spot in their center, or "boomerang-shaped" with a cold spot on the periphery, that usually indicates that the cold spots are slower growing or dead regions of the tumor, Dr Siedschlag reasoned. If true, radiation could be more precisely targeted with intensified irradiation of the fastest-growing regions, helping to minimize irradiation of healthy adjacent tissue.

The data presented by Dr Siedschlag suggested this might be possible. Tumors for 7 of 61 patients in a preliminary study had cold spots, and subsequent surgical examination confirmed that 5 of the 7 cold spots were regions of dead cancer cells, Dr Siedschlag reported.

"By decreasing the doses given to cold spots, one might be able to increase the dose given to the rest of the tumor, while keeping the normal tissue dose constant," Dr Siedschlag said. "Or one could keep the dose given to the rest of the tumor constant, which would lead to less side effects with an identical therapeutic result."

However, 2 of 7 (or 28.5% of) cold spots in the preliminary study were *not* composed of dead tumor cells, raising questions about whether FDG-PET data will prove reliable in identifying which cold spots are appropriate candidates for receiving diminished radiation doses. ■

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